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Leber congenital amaurosis associated with biallelic variant in CEP290: case report

Amaurose congênita de Leber associada a variante bialélica no gene *CEP290*: relato de caso

Daniel Bodour Danielian Filho[1], Pedro Luiz Lage Bodour Danielian[1], Luciene Chaves Fernandes[2], Fernanda Belga Ottoni Porto[3]

1. Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil.
2. Biocor Instituto, Belo Horizonte, MG, Brazil.
3. INRET Clínica e Centro de Pesquisa, Belo Horizonte, MG, Brazil.

KEYWORDS:

Leber congenital amaurosis; Retinal dystrophies; Low vision; Visual stimulation; Ophthalmology.

ABSTRACT

To report a case of Leber Congenital Amaurosis (OMIM 611755). Male patient with nystagmus and low vision since birth. Ophthalmological examination when he was 04 months old showed horizontal nystagmus of moderate frequency and medium amplitude, pupils minimally reactive to light, poor fixation to high-contrast objects and significant decline in visual acuity. Dynamic retinoscopy +4.00 and static +7.00 in both eyes. Fundoscopy in both eyes revealed normal optic nerve head and diffuse loss of pigment from the retinal pigment epithelium. Brain MRI showed signs of neonatal hypoxia in an ependymal line and body of the caudate nucleus on the right, with no signal alteration in optical pathways. Full-field electroretinogram and evoked visual potentials were non recordable. NGS-based molecular investigation identified biallelic variants in *CEP290* gene [c.2991+1655A>G e c.5850delT(p.Phe1950LeufsTer15)]. Correction of refractive errors and early intervention with visual stimulation were prescribed. At the age of 25 months, the nystagmus was reduced and a visual acuity of 0,02 was reached. Leber Congenital Amaurosis is a rare and underdiagnosed disease. A thorough analysis combined with specific propaedeutics, including genetic testing, helps to achieve a diagnosis, a better prognosis and a more effective handling, leading to a better visual development.

PALAVRAS-CHAVE:

Amaurose congênita de Leber; Distrofias da retina; Visão subnormal; Estimulação visual; Oftalmologia.

RESUMO

Relatar um caso de amaurose congênita de Leber (OMIM 611755). Paciente do sexo masculino com nistagmo e baixa visão desde o nascimento. Exame oftalmológico aos quatro meses de idade mostrou nistagmo horizontal de frequência moderada e amplitude média, pupilas minimamente reativas à luz, má fixação a objetos de alto contraste e diminuição significativa da acuidade visual. Retinoscopia dinâmica +4,00 e estática +7,00 em ambos os olhos. Fundoscopia em ambos os olhos revelou cabeça do nervo óptico normal e perda difusa de pigmento do epitélio pigmentar da retina. Ressonância magnética cerebral mostrou sinais de hipóxia neonatal em linha ependimal e corpo do núcleo caudado à direita, sem alteração de sinal nas vias ópticas. Eletrorretinograma de campo total e os potenciais evocados visuais resultaram em não registráveis. Investigação molecular baseada em NGS identificou variantes bialélicas no gene *CEP290* [c.2991+1655A>G e c.5850delT (p.Phe1950LeufsTer15)]. Foi prescrita correção de erros refrativos e intervenção precoce com estimulação visual. Aos 25 meses de idade, o nistagmo foi reduzido e a acuidade visual chegou a 0,02. A amaurose congênita de Leber é uma doença rara e subdiagnosticada. Uma análise aprofundada aliada a uma propedêutica específica, incluindo testes genéticos, ajuda a obter um diagnóstico, um melhor prognóstico e um manejo mais eficaz, levando a um melhor desenvolvimento visual.

Corresponding author: Daniel Bodour Danielian Filho. E-mail: danielbodour98@gmail.com.
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INTRODUCTION

Inherited retinal diseases constitute a vast group of diseases with overlapping phenotypic spectrum and difficult accurate clinical classification. Leber Congenital Amaurosis (LCA) is characterized by typical clinical features, such as congenital and severe visual loss, sensitive nystagmus, possibly altered fundoscopy (depending on the gene), severe hypermetropy, minimal or non-recordable full-field electroretinogram in the first year of life and the presence of Franceschetti's sign. Amongst the early onset inherited retinal diseases, LCA is the most severe, being responsible for 1 in every 5 cases of legal blindness in children and for 5% of all hereditary retinal diseases[1,2]. It is estimated that LCA affects 2-3 individuals in every 100.000[1].

We report herein a rare case of LCA 10 (OMIM 611755) associated with complex heterozygosis of the *CEP290* gene, emphasizing the importance of a prompt diagnosis to allow early visual stimulation and the positive outcomes of a genetic investigation as a way to allow prognostic orientation and genetic counseling.

CASE REPORT

A 4-months-old caucasian male patient was referred because of nystagmus and poor fixation since birth. He presented horizontal nystagmus of moderate frequency and medium amplitude, pupils minimally reactive to light, poor fixation to high contrast objects and significant decline in visual acuity (worse than 0,001). Dynamic retinoscopy +4.00 and static +7.00 in both eyes. Fundoscopy showed normal optic disc and loss of pigment from the retinal pigment epithelium in both eyes. Spectacles +4.00 were prescribed and the patient-initiated follow-up in an early intervention and visual stimulation program. When 09-months-old, the horizontal nystagmus persisted with moderate frequency and amplitude, with slow pupillary reflex, difficulty to fixate on high contrast objects. Visual Acuity (VA) of 0.23cy/cm at 38cm in right eye (OD) and 0.32cy/cm at 38cm in left eye (OS). Dynamic retinoscopy +5.00 and static +7.00 in both eyes. Contrast sensitivity in both eyes showed response to 25% contrast. Spherical lenses spectacles +5.00 with alternate occlusion were prescribed and visual stimulation was maintained. Full-field electroretinography and evoked visual potentials showed no recordable response. Brain MRI at the age of 03 months revealed signs of neonatal hypoxia in an ependymal line and body of the caudate nucleus on the right. NGS screening with a panel of 537 genes identified two variants in the *CEP290* gene[3,4]: **NM_025114.3:c.5850delT(p.Phe1950LeufsTer15)**, inherited from the mother and **NM_025114.3:c.2991+1655A>G**, inherited from the father.

At the age of 25 months old, the nystagmus was reduced and the Franceschetti's sign was positive. VA of 0.64cy/cm at 55cm (0,02) in both eyes and contrast sensitivity with response to 10%. Dynamic retinoscopy +5.00 and static +7.00 in both eyes. Spectacles +5.00 in both eyes were maintained and the occlusion was discontinued.

DISCUSSION

LCA can be classified into non-syndromic, when it occurs with isolated ophthalmological features, or syndromic, when the ophthalmological alterations are combined with systemic symptoms. So far, 24 genes have been associated to LCA. A study conducted in the Brazilian population showed *CEP290* gene in 18% of all the cases of LCA[2,5].

LCA2 (MIM 204100) is caused by bialelic pathogenic variants in the *RPE65* gene. Voretigene Nepavorec is an adeno-associated virus (AAV) vector-based therapy that has been genetically modified to express human *RPE65*. The subretinal injection of the drug results in transduction of some RPE cells with complementary DNA (cDNA) encoding normal *RPE65* protein.

Apart from the LCA2, all others LCA genotypes are considered incurable. Handling consists in treating the symptoms, with a multiprofessional follow-up aiming for visual habilitation. It is also essential to correct associated refractive errors, in order to improve the patient's visual acuity as much as possible. Dynamic and static retinoscopy must be conducted to define the optical prescription. Moreover, it is necessary to prevent secondary complications, with an emphasis on the consequences of the Franceschetti's sign: enophthalmos, cataract and keratoconus. An adequate genetic counseling and ophthalmological longitudinal follow-up are strongly recommended.

In the reported case, the diagnosis was early stablished, enabling a more effective handling, with a more significant visual development and more quality of life. It was revealed that the mean age of the patients with LCA at their first ophthalmological

examination was approximately 2 years old[6]. The early molecular diagnosis allowed specific genetic counseling and confirmed the clinical diagnosis, distinguishing LCA from other retinal dystrophies. Furthermore, a better knowledge about the genetic mutation allows to predict possible systemic diseases associated with mutations in specific genes, such as the *CEP290*, which is related to several systemic diseases.

Variants in the *CEP290* gene contribute to 15-20% of the cases of non-syndromic LCA (LCA10 OMIM611755). The most common variant in this gene is c.2991+1655A>G, found in 57.5%[7] to 87%[8] of the cases[2]. In the LCA10, despite the severely affected photoreceptors since birth as documented by the full-field electroretinogram, optical coherence tomography shows long preserved photoreceptors on the fovea[7-9], which raises expectation to the functional recovery through genetic therapy. The c2991+1655A>G variant in LCA10 leads to the introduction of a cryptic exon and to the consequent loss of 50% of the mRNA reading. This intronic variant is an ideal target for genetic therapy, since preventing the insertion of the X in the CEP290 mRNA could fully restore *CEP290* splicing and the wild-type *CEP290* levels. The editing of the RNA using antisense oligonucleotides to skip exon in order to cancel the disease causing variant, and the correction of the faulty splicing site mediated by CRISPR/Cas-9 are under research for p.Cys998X LCA10. Both therapeutic approaches are promising and under clinical trials. The first genetic editing mediated by CRISPR/Cas-9 in humans via subretinal injection was first conducted at the first trimester of 2020. In this occasion, the result of the phase 1/2a clinical trial was published, in which the effect of the intravitreal injection of antisense oligonucleotide in treating LCA caused by the c.2991+1655A>G intronic variant in the *CEP290* gene was evaluated. This study revealed a significant improvement in the patients' visual acuity, putting an interesting therapeutic possibility into discussion[10].

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AUTHOR'S INFORMATION



» **Fernanda Belga Ottoni Porto**
https://orcid.org/0000-0002-4308-1766
http://lattes.cnpq.br/3705547122177092



» **Luciene Chaves Fernandes**
http://orcid.org/0000-0002-0385-6651
http://lattes.cnpq.br/7701719253016287



» **Pedro Luiz Lage Bodour Danielian**
https://orcid.org/0000-0001-8893-071X
http://lattes.cnpq.br/2187178046446501



» **Daniel Bodour Danielian Filho**
https://orcid.org/0000-0002-2211-029X
http://lattes.cnpq.br/9192036929087702